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REVIEW ARTICLE

Biliary Tree Malignancies

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Radiation therapy is used as definitive treatment for unresectable bile duct tumors, or as adjuvant therapy after resection. External beam irradiation of 45–50 Gy is generally given whenever feasible. Intraluminal brachytherapy is a useful technique to deliver higher doses of radiation to the tumor while respecting the tolerance of the surrounding normal tissues. Brachytherapy can be given at a high dose rate or low dose rate via an in-dwelling biliary drainage catheter to boost external beam doses. Brachytherapy alone is reserved for palliative therapy. Techniques should be implemented with care to make them not only effective but safe. The long-term efficacy and morbidity of this mode of radiation should be studied further. Only large prospective trials can lead to resolution of some of the questions yet unsolved in treatment of these challenging malignancies. *J. Surg. Oncol. 1998;67:203–210.*

KEY WORDS: brachytherapy; biliary neoplasms; radiotherapy; morbidity

INTRODUCTION

Extrahepatic bile duct tumors spread by direct extension either within the ducts or by extraductal involvement of surrounding organs, and they are often multicentric, placing the entire biliary tree at risk. The rich lymphatic network and the thin walls of the extrahepatic bile ducts allow early extension through the walls into the submucosal lymphatics and to lymph nodes in the portahepatis and celiac axis, which are involved in 40–50% of patients [1–3].

Surgical extirpation is the treatment of choice. However, as a result of the pattern of spread of these tumors, 70–80% are unresectable upon presentation [2–4]. Even after successful gross tumor removal, margins are often close or positive, indicating the need for adjunctive radiation to decrease the risk of recurrence [1,2,5]. A median survival of 12–24 months and a 5-year survival of 0–15% is achieved in some resected patients, whereas a median survival of 6 months and a survival of <5% is achieved in unresectable patients [1,3,5–9]. It is locoregional, rather than distant disease that is most often the cause of death, usually as a result of liver failure secondary to progressive obstruction, complicated by cholangitis and sepsis [1,2,5,7,8,10]. Therefore, increasing survival by securing local control should be the objective of treatment, offering an excellent opportunity for surgeons and radiation oncologists to work together toward this goal. These treatment goals must, however, be balanced against the knowledge that, despite aggressive locoregional treatment, many patients will succumb to their disease and that, in realistic terms, treatment will be essentially palliative. Therefore, the duration and morbidity of treatment must be compared with its benefit.

MATERIALS AND METHODS

Radiation therapy (external beam radiation therapy, brachytherapy, or a combination) can be given as definitive treatment for unresectable tumors or as adjuvant therapy after resection.

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Definite External Beam Radiation Therapy (EBRT) and Brachytherapy

The goals of treatment in unresectable disease are, at a minimum, to alleviate pain, to relieve obstruction, to provide tumor regression, and possibly to improve survival. With unresectable disease, the challenge of definitive irradiation is to deliver adequate doses to eradicate gross tumor while respecting the tolerance of the surrounding normal tissues (liver, kidneys, GI tract, and spinal cord). If treatment is with ''curative intent,'' doses in excess of 60 Gy are needed, but this often exceeds the tolerance of the adjacent normal organs. The high rate of locoregional recurrence after definitive EBRT points to the need for techniques to deliver higher doses of radiation. Intraluminal brachytherapy (radiation delivered through the lumens of the bile ducts) may provide this option, providing access and additional dose delivery to the tumor while sparing the surrounding normal tissues [3,7,8,10–57]. EBRT usually precedes brachytherapy [8, 15,16,19,20,22–24,29,30,32,34,36,39–41,43] to decrease tumor bulk before implantation so that residual disease is encompassed by the limited range of the intraluminal radiation. At some institutions, implantation has preceded EBRT [3,10–14,16–19,33,37–38].

In either setting, EBRT doses typically range from 45–50 Gy (Tables I and II). The fields must encompass the tumor with generous margins to allow for undetected spread throughout the biliary tree remote from the tumor. The target volume is often difficult to define due to the intrahepatic spread of these tumors, and radiologic imaging studies including the percutaneous transhepatic cholangiograms (PTC), computerized axial tomography (CAT), magnetic resonance imaging (MRI), ultrasound, and Endoscopic Retrograde Cholangiopancreatography (ERCP) should be used whenever possible to define suitable radiation portals. In addition, the intraoperative findings also should be communicated to the radiation oncologist to help define the irradiated volume. Surgeons should be made aware that placement of surgical clips at tumor margins or around unresectable tumor is invaluable for treatment planning.

Adjuvant EBRT and Brachytherapy

Whenever possible, resection should be attempted. After this, every attempt must be made to enhance the durability of locoregional control. To this purpose, both EBRT and brachytherapy may be combined to minimize late complications and to target areas where margins may be close or positive [3,7,8,10–21].

Brachytherapy Alone

A third treatment option for stented patients is intraluminal irradiation alone. Because this approach has certain limitations (i.e., bulky tumor will not be encompassed by the limited penetration of the intraluminal sources), brachytherapy alone is reserved for palliation [3,7,8,10–14,16–21,25–28,30–32,34,37,38,42–44,50].

Brachytherapy Techniques

Intraluminal brachytherapy is particularly suited to this disease site as one can take advantage of the anatomical lumens where these tumors originate to place radioactive materials. Plastic catheters can be placed at the time of radiologic studies, laparotomy, or endoscopy for external or internal biliary drainage and are used to provide access to the biliary tract. These catheters are later loaded with radioactive sources. Radium sources were used initially [47]. Currently, low dose rate (LDR) iridium-192 and, more recently, high dose rate (HDR) iridium-192 and cobalt-60 sources have been used. The LDR and HDR techniques differ in the total dose delivered, dose-rate (dose per unit time), number of fractions, and duration of treatment. The advantages of low dose rate irradiation are that typically only one insertion and a smaller diameter catheter (8–10 Fr) are required. Inpatient care over the 24–72-hour-long implant and radiation exposure to caregivers are inherent disadvantages, as is the potential for interference with bile drainage while the sources occupy the drainage catheter. High dose rate techniques that deliver radiation over several minutes are given on an outpatient basis with complete radiation protection for individuals involved, with the added advantage of optimization of the dose distribution. Also, the likelihood of catheter-related sepsis and catheter dislodgement is minimized; however, multiple insertions through a larger catheter (10–14 Fr) are required. In cases in which the high dose rate source cannot negotiate sharp curves within the catheterized biliary system, an LDR technique is required [19,42,43].

Percutaneous Transhepatic Catheter Placement

The percutaneous transhepatic technique is the technique most commonly used to deliver intraluminal radiation at our institutions and is recommended. Transhepatic percutaneous catheter insertion (ring, pigtail) entails guiding a catheter into the dilated intrahepatic bile ducts, through the obstructing tumor, and into the duodenum, over a guidewire positioned during percutaneous cholangiography. This procedure provides both internal biliary drainage across the tumor and external drainage via the proximal end of the catheter [32,48,51].

Before intraluminal irradiation, it is helpful for the diagnostic radiologist, gastroenterologist, or surgeon to review the pretreatment cholangiogram and ERCP with the radiation oncologist and identify the site and length of obstruction. It is important to verify that a biliary drainage catheter of adequate diameter (usually No. 12–14 Fr for HDR and No. 8–10 Fr for LDR) is in place to accommodate the brachytherapy catheter. Using sterile

TABLE I. Extrahepatic Bile Duct—Low Dose Rate Series

Author	N	Ext xrt	I.C. dose prescription	Local control	Survival	Complications
Wheeler et al. [26]	5	Ext & I.C.—1 I.C. only—4	4000–4800 cGy/48 hr at 0.5 cm from source at 83–100 cGy/hr	2/8 (25%)	11 mo med 2 pt NED-2 yrs	
Fletcher et al. [27]	18	0	Mean = 4470 cGy/55.3 hr at 0.5 cm from source at 80 cGy/hr		11 mo. med. 9 pt surv ⩾12 mo	
Karani et al. [28]	30	0	4000–5000 cGy/48 hr at 0.5 cm from source at 83–104 cGy/hr		Median = 16.8 21 pt alive >1 yr 5 pt alive ⩾2 yr	
Chitwood et al. [3]	16	4600 cGy/23 FX—7 I.C. only—3	5000 cGy/21–100 hr at inner surface of bile duct (Effective dia = 1.0 cm)	6/10 (60%) at 3–13 mo	5/10 alive 1–12 mo	0
Jones et al. [12]	10	3600–5000 cGy-7; I.C. only-3	4750–10,000 cGy/21–162 hrs calc radius of 1.5–5.8 mm	6/10 (60%) at 3–13 mo.	5/10 alive at 6–26 mo.	0
Herskovic et al. [13]	16	None or 3600–5000 cGy Ext & I.C.—12 I.C. only—4	1060–10,000 cGy at 0.5 cm from source at 37–240 cGy/hr	13/16 (81%) 3 marginal recurrences	1 pt NED 15/16 dead 10/16 D$\overline{C}$D	Cholangitis-5; Duodenal & gastric ulcers-2
Meyers and Jones [14]	27	3000–4500 cGy—22; I.C. only—5	3000–5000 cGy at 0.5 cm from source		Median surv 11.5 mo. I.C. only = 3.6 mo I.C. & EXT = 14.3 mo	Cholangitis-21/27; Hemobilia-4 Abscess-9; Choledochoduodenal fistula-1
Hayes et al. [30]	10	4100–6020 cGy—8; I.C. only—2	1310–5800 cGy at 0.5 cm from outside of catheter		I.C. only 11.9 & 13.8 mo Ext & I.C. 13.2 mo (7.4–30.3)	Sepsis-75%; Cholangitis-62%; Abscess-30%; GI bleed-50%; Hemobilia-38%; Duodenal ulcer-38%; Gastric outlet obstruction-25%
Veeze-Kuijpers et al. [16]	30	3000–4000 cGy—26; I.C. only—4	1500 cGy × 2/75 hr at 1 cm from source or 2500 cGy × 1 at 1 cm from source at 20 cGy/hr		Median = 10 mo 16% at 3 years	Cholangitis-6/38; Gastritis and duodenal ulcers-3
Ede et al. [31]	14	0	6000 cGy/85 hr at 0.5 cm from source at 71 cGy/hr		10.5 mo after implant	Cholangitis-2
Flickenger et al. [8]	12	None or 2600–6000 cGy Ext & I.C.—9 I.C. only–3	I.C. only: 2800–5500 cGy at 0.5 cm from source; boost: 1400–4500 cGy at 0.5 cm from source			
Mahe et al. [10]	25	4250 cGy (17 pts)(Curative)	I.C. only—3000–6000 cGy at 0.5–1 cm from source;		Gross resection, 2 pts	Cholangitis-3
Gerard et al. [18]		2000 cGy/5 FX—(Palliative); I.C. only—8	Boost—1000–3000 cGy at 1 cm from source		Ext & I.C D$\overline{C}$D 7-14 mo; 2 pt I.C. D$\overline{C}$D 58 & 60 mo	
Gonzalez et al. [7]	27	I.C. & Ext—23 I.C. only—4	1.0 cm from source		Median survival 18.7 mo with Ext & I.C. Xrt after resection (15 pts) and 12.3 biliary drainage—(9 pt)	Duodenal ulcers-5 Pyloric stenosis-3

*D$\overline{C}$D = dead with disease; D$\overline{S}$D = dead without disease; Def = definitive irradiation; Dia = diameter; Ext = external beam; IC = intracavitary; IR = iridium 192; N = number of patients; NED = no evidence of disease; Perc = percutaneous; Postop = postoperative irradiation; TID = three times per day; X = fraction; Med = Median.

TABLE II. Extrahepatic Bile Duct—High Dose Rate Series*

Author [ref]	No. of pts	Ext xrt	IC dose prescription	Activity	Local control	Survival	Complications
Yoshimura et al., 1992; RALS [41]	15	3000–3200 cGy	3000–6000 cGy/4–6 FX/2 per week at 1 cm from source	4 Ci Co60	Tube Free—7 mo; 12/13 able to d/c perc tube	Ave = 9.0 mo 2/15 alive at 26.8 & 32.2 mo after XRT	Hemobilia—1
Pavlou et al., 1990 Nucletron [19]	8	None or 4500 cGy	No Ext: 3000 cGy/6 FX; Ext: 2000 cGy/4 FX or 3000 cGy/5 FX or 1000 cGy/3 FX; at 1 cm from source	10 Ci Ir-192			0
Nori et al., 1993 [43]	15	None or 4500–5000 cGy	1500–2000 cGy/3–4 FX If no Ext: 3000 cGy/6 FX; at 1 cm from source	10 Ci Ir-192		8 NED at 6–24 mo	Sepsis—1
Pakisch et al., 1992 Nucletron [44]	9	5040 cGy—6 IC only—3	1000 cGy at .75 cm from source	10 Ci Ir-192	9/9 maintenance of bile flow 7/9 palliated for 7.5 mo	7.5 mo	
Ryu et al., 1988 RALS [21]	6	5000 cGy—4 IC only—2	500 cGy × 5 at 1.5 cm from source	4 Ci Co60	5/6 resolution of stricture		
Classen and Hagenmuller, 1987 [55]	17		3000 cGy at 1 cm from source	10 Ci Ir-192		Def Xrt—3 mo Postop Xrt—1 D$\bar{s}$D at 7 mo, 1 NED at 9 mo	

*D$\bar{c}$D = dead with disease; Def = definitive irradiation; D$\bar{s}$D = dead without disease; Dia = diameter; Ext = external beam; IC = intracavitary; NED = no evidence of disease; Perc = percutaneous; Postop = postoperative irradiation; TID = three times per day; X = fraction.

precautions, the biliary drain is opened, the orifice cleaned, and the catheter is flushed with sterile normal saline. A sterilized blind-ended brachytherapy catheter (with a stainless steel guide-wire/obturator that prevents kinking) is inserted into the drainage catheter and advanced to the desired position in the biliary tree under fluoroscopy, often using biliary contrast to define the stricture. The guidewire is then replaced by a ''dummy source train'' (nonradioactive wire). Orthogonal radiographs for computerized dosimetry (radiation planning) are taken (Fig. 1) and the target length to be irradiated is determined, factoring in a sufficient margin (usually 2–3 cm) on either side of the stricture.

In the LDR technique, the iridium ribbon or wire is then manually inserted into the location in the biliary tree determined initially with the dummy sources for LDR techniques and the iridium source train is secured in place for the duration of the implant. The source train and catheter are subsequently removed at the bedside after the typical 24–72 hour implant. For high dose rate implants, the brachytherapy catheter is connected to the remote afterloading device and the treatment is delivered over several minutes in a shielded room. After treatment delivery, for both HDR and LDR techniques, the catheter is removed, and the biliary drainage catheter is flushed and capped. The patient is discharged home on antibiotics (oral ciprofloxacin) to reduce the risk of cholangitis with recommendations for temperature monitoring.

Endoscopic Catheter Placement

Catheter insertion through stents or prosthesis also can be accomplished endoscopically by a gastroenterologist at the time of the ERCP [7,19,31,33,37,42–44,49–50,53–55]. Typically, the biliary system already has been evaluated by ERCP and a sphincterotomy performed to provide access for a large caliber prosthesis [31,33,49,54]. An extra-long (130–150 cm) catheter (10–14 Fr) is inserted transorally through the duodenum into the bile duct via the sphincterotomy and is advanced through the malignant stricture. One disadvantage of the endoscopic approach is that a pre-existing stent must be removed, necessitating another ERCP to replace the stent after irradiation and posing further risk associated with additional sedation and failure subsequently to replace the

Fig. 1. Localization radiographs of patient with dummy sources in afterloading catheters placed through the left and right hepatic ducts into the common bile duct to treat tumor at the bifurcation of the bile ducts. Target area to be irradiated is indicated by arrows.

stent. Furthermore, it is sometimes difficult for the HDR source to negotiate the duodenal-ampullary curve. For these reasons, the transhepatic approach is often preferred for both LDR and HDR insertions.

Intraoperative Catheter Placement

Biliary catheters (T-tubes, U-tubes, Y-tubes, silastic transhepatic biliary stents) placed by surgeons intraoperatively, after biopsy, bypass, or resection also can be used for intraluminal brachytherapy [4,6,25,48]. It is important for the radiation oncologist to discuss with the surgeon the location of the catheters in relationship to the tumor or tumor margins and segments of the GI tract so that sources can be placed strategically. When remote afterloading techniques are used, the surgeon also should be aware of the difficulties in loading acutely angled afterloading catheters.

Dose/Fractionation Schemes

Fraction size and total intraluminal dose vary by series, depending in part on the use of EBRT and upon whether LDR or HDR techniques are implemented (Tables I and II). The High Dose Rate Brachytherapy Working Group (HIBWOG) has proposed a dose of definitive EBRT of 45 Gy with an HDR brachytherapy boost of 20 Gy (5 Gy × 4) specified at 1 cm from the source. For palliative intraluminal irradiation, 30 Gy (5 Gy × 6) (HDR) was proposed [43]. For LDR, we use 25–30 Gy brachytherapy (at 1 cm) to boost 45–50 Gy EBRT for definitive treatments and 40 Gy LDR brachytherapy alone for palliation [43].

RESULTS

Local Control

Long-term local control is an important end-point in this disease and is achievable in some patients [3,11–13,22,23,25,26,29,35,38,50]. Relief of biliary obstruction, evidenced by a decline in liver enzymes and jaundice and improved quality of life, is one cited palliative endpoint [3,11,25,37]. However, it is difficult to distinguish the contribution of the drainage catheter from that of the brachytherapy. Whether the biliary drainage catheter can be discontinued after irradiation is unclear. Pakisch et al. [44] noted unrestrained bile flow in all nine patients treated with definitive intraluminal HDR with or without EBRT, with palliation lasting as long as the survival time (7.5 months) in 7 of the 9 patients. Yoshimura et al. [41] reported an average tube-free period of 7 months after definitive intraluminal HDR with or without EBRT, with 12 of 13 patients who were treated able to discontinue percutaneous drainage.

Survival

There is some suggestion that the patency of drainage secured by radiation may enhance survival. Wheeler et al. [26], using definitive external and intracavitary vs. intracavitary irradiation alone, suggested that radiation enhanced the effect of tube drainage, giving a significantly increased chance of surviving nine months than with surgical drainage alone ($P<0.01$). Radiation was concluded to improve survival over bile drainage alone, with a median survival of 11 months and with two patients NED at 2 years [25,26]. In a follow-up of the Wheeler series, a mean survival of 16.8 months (1–66 months) was achieved with the addition of intraluminal irradiation, and survival time compared to that associated with bypass surgery or percutaneous biliary drainage alone was doubled [27,28,48]. Jones and others [3,11,12] noted a mean survival of 10.6 months in patients stented and irradiated (postop and definitive) vs. 3.5 months for those with stenting alone [3,11,12].

As shown in Tables I and II, survival seems to be increased, although not in all series, in patients who have undergone resection and have subsequently received postoperative irradiation. Gonzalez et al. [7] noted a median survival for surgery alone versus surgery and post-

operative irradiation of 8.25 and 19 months, respectively, and 1-, 2-, and 3-year survival rates of 36%, 18%, and 10% for surgery alone versus 85%, 42%, and 31% for surgery and postoperative irradiation ($P = 0.0005$). Survival was also superior to that of patients who were treated with biliary drainage and irradiation, with a median survival of 12.3 months with 1-, 2-, and 3-year survivals of 46%, 15%, and 12% [7].

Data supporting the ability of the combination of external and intraluminal brachytherapy to enhance local control and survival through delivery of higher doses are inconclusive [7]. There is a suggestion that the combination may be superior to EBRT alone, perhaps because of the higher cumulative doses delivered [14,15,22,30]. Long-term survival of patients treated with a combination of EBRT and brachytherapy boost has been reported [17,20,35–37,41,43].

Complications

The frequency of complications after irradiation is recorded in Tables I and II. Transient cholangitis is the most frequent complication after intraluminal irradiation. Fatal sepsis, perihepatic abscesses, excessive bleeding, hemobilia, and GI tract injury are most often observed when both external and intracavitary irradiation are combined [7,13–16,22,29,30,34,35,37,38,41,57].

DISCUSSION

Considering the known spread pattern of these lesions throughout the biliary tree and to the regional lymphatics, it would seem that using a combination of EBRT to treat the primary tumor and adjacent tissues at risk and intraluminal radiation to ''boost'' the bulky luminal and periluminal disease or areas of close or positive margins to higher doses would be a reasonable approach [2]. This will allow a decrease in the external dose, thereby minimizing side effects, and it will shorten the course of treatment for these patients who have a limited survival. The major problem with exclusive intraluminal irradiation is that the diameter of irradiated volume measures only 1–2 cm, but the tumor volume often exceeds this range [38]. Hence, brachytherapy alone is to be used only as a palliative measure, whereas EBRT is to be added to treat the entire target volume, and the brachytherapy is to be used as a boost in definitive treatments.

Survival appears to be closely related to surgical intervention that is dictated by tumor extent at presentation: laparotomy alone, mean survival of 5.6 months; stenting with a Y- or T-tube, mean survival of 9.9 months; transhepatic stenting, mean survival of 18.6 months; tumor resection, mean survival of 22.2 months [3,6,7,9,18,46]. The impact of radiation on survival is debated. Selection factors may affect the choice of therapy and lead to differences in survival. In the largest series of patients reviewed, Gonzalez et al. [7] reported the results of various treatment regimens for 112 patients with proximal bile duct cancer treated at seven European institutions (mean or median survival after resection with positive margins = 7–23 months and a 3-year survival rate ranging from 10–18%). Adding their series to other series in the literature, the mean survival was 13.9 months +5 months with a mean survival at 3 years of 13% in 179 patients. In 79 patients, who subsequently received adjunctive postoperative irradiation, the median or mean survival varied from 15.7–28 months with a 3-year survival rate between 25–31% and a mean survival of 21.5 months +5 months. Patients with tumor resection and postoperative irradiation had a significantly better survival rate than those treated with surgery alone or with biliary drainage and irradiation. No conclusion could be reached about the addition of intraluminal irradiation. In a review of the literature of 300 patients treated with biliary drainage and irradiation without resection, the median or mean survival varied from 7–27 months with survival rates at 1 and 3 years varying between 10–63% and 0–30% and a mean survival of 12.5 months +4–8 months versus 10 months without the addition of radiation [7].

There is little information in the literature concerning complications associated with long-term percutaneous biliary drainage, regardless of intraluminal brachytherapy. Hemobilia, cholangitis, and intrahepatic abscesses have been reported apart from radiation, and the impact of radiation on their development is unknown. The risk of cholangitis with endoscopic techniques appears to diminish if radiation is delayed at least 2 weeks after biliary endoprosthesis insertion [56]. The use of antibiotics 12–24 hours before and 48–72 hours after catheter manipulation or replacement is recommended. Patients with subsequent signs of cholangitis should be treated with antibiotics for 10–14 days. Frequent tube irrigation without aspiration (organisms drawn from GI tract) with clean techniques are recommended. Fever developing in this setting usually means that the tube has become occluded with sludge or dislodged and needs cleaning or replacement. Oral antibiotics are then prescribed, and fevers should subside within 24 hours. Prolonged fever should raise the suspicion of liver abscess, the frequency of which is increased after 8 months of external drainage, and the patients should be admitted for workup and potential drainage to avoid fatal sepsis [30,52].

Radiologic studies often demonstrate biliary stenosis after radiation. Radiation-induced stricture formation is of concern particularly when intraluminal techniques are used, and the question of whether, after radiation, a malignant stricture is not simply replaced by a fibrotic stricture is important since all such strictures may be life-threatening. Nag [32] speculates that intraluminal brachytherapy may lead to ductal fibrosis and strictures

and recommends leaving the catheters in place several months after intraluminal therapy to avoid this. If the patient is anxious to have external drainage catheters removed, it is possible to convert from external to internal drainage. Strictures may develop and may require dilation or reintubation of the ducts [13].

Additional areas of investigation include the use of hyperthermia in association with intraluminal iridium, extensive liver resection, liver transplantation, and whole liver irradiation [58–60] as well as the role of chemotherapy [1,2,4,5,7,8,10,14,15,17,22,24,29,34–36,43,45,50].

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